REMARKS

Claims 1, 2, 4-6 and 8-20 are in the application. Claims 7 and 21-33 have been previously canceled. Claim 3 is presently canceled. Claims 1, 4, 5, 14, 15, 19 and 20 are amended. No claim is allowed.

Claims 1, 2, 4-6, 8, 10, and 15 are rejected under 35 USC 102(b) as allegedly being anticipated by Cook *et al.* '585 (Cook). This rejection is respectfully traversed. Claim 1, as amended, clarifies that the matrix comprises two layers, each layer of which can be a covalently cross-linked protein, a covalently cross-linked polysaccharide or a protein cross-linked to a polysaccharide. These features are not shown in Cook. The Examiner cites Cook, Example 26, as an embodiment of a cross-linked protein (BSA) layer in a matrix. However, Example 26 does not disclose a cross-linked protein layer. Referring to column 5, lines 35 through 54, which contains a description of the addition of BSA to the membrane, it can be seen that BSA molecules are randomly attached to the top layer of the membrane. See the item labeled "B" in all of the Figures, representing the protein (bioactive species). The top layer is polyethyleneimine (PEI), which is neither a polysaccharide nor a protein. The BSA is neither cross-linked to itself nor is it a layer. The Examiner further states that in Example 26 the protein and polysaccharide are cross-linked to each other with glutaraldehyde. This is not the case. The protein, BSA, is attached to the top layer of PEI, which is not a polysaccharide. In example 3, column 17, lines 31-36, the glutaraldehyde is used, before any protein or other bioactive species is attached to the membrane, to cross-link the PEI, which contains free amino groups with which the glutaraldehyde cross-linking agent can react. The PLA:PGA (polylactic acid:polyglycolic acid) substrate of the membrane does not contain reactive side chains, so it is not cross-linked by the glutaraldehyde. Thus, nowhere in Cook is there disclosed a matrix comprising two layers where each layer is a covalently cross-linked protein, a covalently cross-linked polysaccharide or a protein cross-linked to a polysaccharide. The most relevant example cited by the Examiner is Example 26. However, Example 26 seems to teach, in order, first a support member of PLA:PGA, which is not a cross-linked polysaccharide or a cross-linked protein. Secondly, there is a layer of PEI. According to Cook's claim 7, one might replace the PEI with hyaluronic acid, which is a polysaccharide. However, as discussed above, the BSA is merely randomly attached to the surface PEI, and is not itself a cross-linked layer. Therefore, Cook discloses a membrane

with a cross-linked polysaccharide layer. But a second layer which is a cross-linked protein, cross-linked polysaccharide or a protein cross-linked to a polysaccharide is absent. Thus, none of the structures disclosed in Cook anticipates the present claims and withdrawal of the rejection is respectfully requested.

Claims 1, 2, and 5 are rejected under 35 USC 102(b) as allegedly being anticipated by Schwartz *et al.* '997 (Schwartz). This rejection is respectfully traversed. The Examiner suggests that the material of Schwartz is cross-linked, citing column 7, lines 53-57. While the term cross-linking is utilized in that passage, upon closer examination, it is seen that the carboxypolysaccharide and the polyether components in the material of Schwartz are only associated as a complex through hydrogen bonding. Present Claim 1, as amended, recites that the polymeric component within the multi-layer matrix is covalently cross-linked. The polymeric components within the material described by Schwartz are not covalently cross-linked. Therefore, Schwartz does not anticipate the claims and this rejection should be withdrawn.

Claims 1-6, 8, 10, 11, 13, 15, and 16 are rejected under 35 USC 102(b) as allegedly being anticipated by Yannas '289 (Yannas). Yannas is directed to the preparation of a blood vessel prosthesis having a multi-layer tubular structure. The preferred materials for the layers consist of collagen molecules or collagen fibrils cross-linked to aminopolysaccharide chains. See column 3, lines 24-31. However, the prosthesis must have low porosity to prevent leakage of whole blood and blood componenets. See column 2, lines 16-23 and col. 6, lines33-37. This means that the pores exclude passage of living cells. The pores are less than 10μ in size. See col. 6, line 34.. However the matrix comprising the layers according to the present invention has porosity sufficient to allow living cells to pass. See page 4, lines 8-9; page 6, lines 27-28; page 12, lines 16-26. Accordingly, it is submitted than Yannas does not anticipate the present claims.

Claims 1, 6, and 18 are rejected under 35 USC 102(b) as allegedly being anticipated by Boyce '900 (Boyce). This rejection is respectfully traversed. Boyce is directed to a composite skin replacement material consisting of a biological epidermal component (epithelial cells) and a biosynthetic, acellular, porous, resorbable, dermal membrane component. The membrane component is formed by cross-linking two substances to each

other, collagen and a mucopolysaccharide. See column 7, lines 7-16. The dermal membrane component may be surface-laminated. See col. 5, ll. 39-42; col. 7, ll. 45-59; col. 9, ll.48-64; col. 12, ll.10-13; col. 13, ll. 26, 34; col. 21, l. 48; col. Ll. 21-34. The laminate restricts migration of the cells into the porous dermal membrane. See col. 7, ll.45-59; col. 12, ll. 10-13. Therefore the laminate is sufficiently non-porous to restrict sells. The present claims recite that the layers are sufficiently porous to accommodate living cells. Accordingly, the present claims are not anticipated by Boyce and withdrawal of the rejection is respectfully requested.

Claims 1-6, 8, 9, 12, and 14-17 are rejected under 35 USC 103(a) as allegedly being unpatentable over Hook *et al.* '989 (Hook) and Liu *et al.* '385 (Liu) in view of Schwartz. This rejection is respectfully traversed. The Examiner states that Hook teaches a cross-linked polymeric component comprising the protein collagen, among other proteins (column 2, lines 62-65), and alginate (column 3, lines 3-5), where the linking agent is divinylsulfone. No porosity is disclosed. There is no mention whether pores are present or even desirable. The layer is applied as a gel then air-dried. This would seem to form a non-porous film, although, as previously mentioned, there is no discussion of porosity. The dry film is only intended to be in place on the skin for a period of 20-30 minutes, so accommodation of living cells within the film would not seem to be required, although no mechanism of action is discussed. The Examiner cites Liu to teach a cross-linked polymer component comprising hyaluronic acid or other polysaccharides and collagen. The Examiner relies on Schwartz to show the advantages of using a multi-layered matrix to manipulate the components and ingredients in each layer to exhibit different properties. As discussed above, Schwartz teaches a material in which a membrane is formed by a polyether and a carboxypolysaccharide associated through hydrogen bonding. Therefore, the membrane in Schwartz is not covalently cross-linked. By combining the references as suggested by the Examiner, one does not arrive at the presently claimed multi-layer matrix. Even if one of ordinary skill in the art would make a multi-layer matrix, the combination of Hook's and Liu's materials as layers would not result in a structure recited in the present claims. Schwartz does not teach which properties to select for each layer. In particular, Schwartz does not teach that each layer should be porous enough so that the matrix can accommodate living cells. Therefore, it is submitted that the combination of references does not form a *prima facie* case. It is thus

submitted that the claims are unobvious over the combination of references and it is respectfully requested that the rejection be withdrawn.

It is submitted that entry of this amendment places the application in condition for allowance.

Respectfully submitted,
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